

Remarks

Claim 1 has been amended to capture the classes of compounds for which the applicants have demonstrated evidence of unexpected results. Support for this amendment is found throughout the application. See the working examples as well as page 5, lines 9, 17-18 and 21, and page 7, lines 9-11 and 13-15. Claim 34 has been amended to be independent by adding the relevant recitations of previous claim 1 and in accordance with the Office Action dated August 29, 2003, is now allowable.

Claim Objections

Amended claim 1 recites haloalkyl, which at page 5, line 18 of the specification, is explicitly exemplified with trifluoromethyl. Therefore, claim 11 is in proper dependent format.

Rejections Under 35 USC103(a)

Obviousness over Mokrosz

Mokrosz discloses compounds without substituents on the phenyl ring. Applicants have previously presented comparative data showing superior properties for compounds in which the phenyl ring was substituted by F, Cl, Br, Me, Et, CF₃, OCF₃ and/or MeS and have amended the claims to capture the classes of compounds for which the applicants have demonstrated evidence of unexpected results. The efficacy of the compounds of the present claims is supported by the data submitted to the PTO on December 6, 2002 and April 24, 2003.

Applicants wish to address one point of the Examiner's argument which is of particular concern. At the bottom of page 4, the Examiner states "Additionally, applicants should note the prior art N-ethyl piperazine as shown by Mokrosz *et al.* is active at the 5HT receptor and hence one would be motivated to make and evaluate the compound with a methyl group in the ring." This allegation has no foundation because the methyl substituent is unexpectedly superior and applicants have already shown this by the comparative data previously submitted.

Obviousness over Jonas (US-3853878) in view of Mokrosz

The Examiner combines an intermediate from Jonas with the disclosure of Mokrosz and concludes that the Jonas and Mokrosz combination would lead the skilled person to the present invention.

Applicants contend that this rejection is improper because the Examiner has not shown that one of ordinary skill in the art would have had the requisite motivation to combine these references. There is no suggestion at all in Jonas that the methoxy-substituted intermediate compounds were pharmacologically active. Jonas teaches that the pharmacological activity requires the presence of the N-carboxamidine group on the pyrazino ring which is absent from Mokrosz's compounds, and absent from the compounds of the present invention. Because Jonas makes no suggestion for the pharmacological use of the intermediates which have no carboxamidine on the pyrazino ring, the skilled person would not consider that these intermediates were active. As such, there is nothing which would teach one of ordinary skill in the art to modify the compounds of Mokrosz by putting a methoxy substituent on the phenyl ring as taught by Jonas. Equally, there is nothing taught by Mokrosz which would suggest to one of ordinary skill in the art that he should modify Jonas's active compounds by removing the carboxamidine group.

The Examiner's comment that "The combined art teaches equivalency of the intermediate compounds with bioactive compounds and hence its pharmaceutical composition" is without foundation.

Moreover, Jonas teaches the use of his compounds for their blood-pressure lowering properties. Mokrosz teaches that his compounds are active at 5HT receptors. There is nothing in either of these two documents which would suggest activity in the target disorder of the other, which is a further reason why there is no motivation to combine the two disclosures.

In summary, there is no motivation for one of ordinary skill in the art to modify the compounds of one document in view of those of the other document in a manner which would result in the compounds of the present invention.

Obviousness over Bos in view of Mokrosz

The Examiner refers to "Bos CA 2097," which applicants presume to mean CA-2097465. Bos teaches tetrahydropyrazinoindoles, whereas Mokrosz teaches tetra- and hexahydropyrazinoindoles. Applicants traverse the Examiner's allegation that: "there is

a clear-cut teaching of equivalency of both tetrahydropyrazinoindole and hexahydropyrazinoindole in their activity toward 5HT" for the reasons that follow.

A structural difference of the presently claimed compounds over those of Bos is that the C-10 position in the presently claimed compounds is saturated whereas the compounds of Bos contain a double bond in this position.

The Examiner says that the teaching of Mokrosz would motivate the skilled person to modify the compounds of Bos in a manner which would result in the presently claimed compounds, i.e. by saturating this double bond. A careful review of the prior art shows that this is not the case for the following reasons.

When one compares compounds (5) and (6) of Mokrosz, which both have an unsubstituted (-NH) group in the piperazine ring, it can be seen that the unsaturated compound (5) has a K_i (5HT₂) of 1800nM whereas the saturated compound (6) has a higher K_i (5HT₂) of 3570nM. In addition, when compounds (7) and (8) are compared, which both have an -N(Et) group in the piperazine ring, it can be seen that the unsaturated compound (8) has a K_i (5HT₂) of 3610nM whereas the saturated compound (7) has a higher K_i (5HT₂) of 3780nM. In both instances, therefore, the saturated compound has a higher K_i and is therefore less strongly binding than the unsaturated compound.

Accordingly, one of ordinary skill in the art, starting from the disclosure of Bos as the closest prior art, would not be motivated to modify the compounds of Bos on the basis of Mokrosz because Mokrosz shows that removing the unsaturation leads to a reduction in the binding affinity. Thus, a combination of Bos and Mokrosz would not lead one of ordinary skill in the art to the compounds of claim 1. Therefore the claimed subject-matter is, *prima facie*, non-obvious.

Respectfully submitted,

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